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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,644	10/29/2003	David S. Garvey	102258.133 US2	4077

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EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,644	GARVEY, DAVID S.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *93-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I in paper filed on April 1, 2005 is acknowledged. Because applicant did not specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse; see MPEP 818.03(a).

2. Claims 1-108 are pending in the application. Claims 93-108 are withdrawn from further consideration as being directed to non-elected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 6-73 and 76-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hypertension using compounds of formulae I, IV and V alone, does not reasonably provide enablement for treating and/or preventing every known vascular disease using compounds of formulae I, IV and V alone or in combination with other compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:

Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on atleast four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, the state of the prior art and the breadth of claims.

The instant compounds are directed to nitrosated and/or nitrosylated nebivolol. In the prior art, the utility of nebivolol as an antihypertensive agent is well established based on its beta-adrenergic antagonist activity. However, there is no teaching in the specification or prior art that nebivolol is well known to have therapeutic utility in treating and/or preventing every known vascular disease and furthermore, there is also no teaching that niric oxide insufficiency is involved in the etiology of every known vascular disease. It is well known in the art that there are multiple mechanisms responsible for the etiology of any known disease condition and therefore, correcting one mechanism (such as beta adrenergic receptor antagonism in the instant case) will not prevent (completely cure) that specific disease condition. There is no teaching or guidance in the specification how the instant compounds having beta- adrenergic receptor antagonist activity will be able to prevent all known vascular diseases. There are no working examples present either in the specification or prior art references mentioned in the specification showing efficacy of nebivolol alone or in combination with any other drug in known animal models of every known vascular disease condition. The instant

compounds of formulae I, IV and V encompass hundreds of thousands of compounds based on the values of variables D, D1, D2 and R6 and therefore, in absence of such teachings and guidance, it would require undue experimentation to demonstrate the efficacy of instant compounds alone or in combination with thousands of drugs (mentioned in claims 15-92) in known animal models of every known vascular disease and hence their utility for treating these disease conditions.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 6, 7, 15, 19, 24, 25, 33, 34, 39, 40, 48, 50, 51, 59, 61, 62, 76, 78, 79, 80, 84, 87 and 90-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 2, it is not clear where the NO or NO2 group is attached to the structure of Nebivolol.

In claims 6, 24 39, 50 and 61 the term ---preventing---is indefinite since the degree of prevention (20%, 40%, 60%, 80% or 100%) is not defined and furthermore, how this prevention is being assessed in vivo? Also, the term –vascular disease characterized by nitric oxide insufficiency —is indefinite since specific disease conditions are not defined. The applicants are suggested to change the term –characterized by ---- to ----due to---.

In claims 7, 25, 40, 51 and 62, the applicants are suggested to change the term – characterized by ---- to ------due to---.

In claims 15, 76, 90 and 92, the specific compounds which donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide etc. are not defined.

In claim 19, the specific compounds comprising ON-O, ON-N- etc. are not defined.

In claims 33, 34 and 91, the specific antioxidant is not defined.

In claim 48, the specific nitrosated compound is not defined.

In claims 59 and 91, the specific compound used to treat cardiovascular disease is not defined. Also, the term---used to ---- is vague. Does it mean that this compound does not treat cardiovascular disease now?

In claim 70, the specific diuretic compound is not defined.

In claims 78 and 79, the target site is not defined and furthermore, how the delivery of nitric oxide to this site is assessed following in vivo administration?

In claim 80, the term –medical device--- is indefinite since specific device is not defined.

In claim 84, the term ---prevention--- is indefinite since the degree of prevention (20%, 40%, 60%, 80% or 100%) is not defined and furthermore, how this prevention is being assessed?

In claim 87, the specific injured tissue is not defined.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Lommen (U.S. Patent 4,654,362, cited on applicants form 1449) in view of Loscalzo (U.S.Patent 6,635,273).

Van Lommen discloses Nebivolol (see compound 84 in column 21 and claims 1-12) for treating hypertension and disorders of coronary vascular system (see col. 5, lines 58-66). Van Lommen differs from the instant claims that it does not teach nitrosated and/or nitrosylated Nebivolol. However, Loscalzo teaches method of treating vascular diseases due to nitric oxide insufficiency by administering nitrosated beta-adrenergic blocker (see col. 2, lines 25-51 and claims 29-31) and further teaches Nebivolol as one of the beta-adrenergic blocker (see col. 6, line 43). Therefore, one skilled in the art would have been motivated to select nirosated Nebivolol as beta –adrenergic blocker for treating vascular diseases since Von Lommen teaches increased beta-adrenergic blocking activity of Nebivolol as compared to other known beta-adrenergic blockers (see col. 1, lines 18-22) either alone as taught by Van Lommen or in combination with antioxidant and/or isosorbide mononitrate or isosorbide dinitrate as taught by Loscalzo.

10. Claims 1-92 are objected for containing non-elected subject matter.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

C. S. Aulakh

Charanjit S. Aulakh
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Art Unit 1625